An Efficient Synthesis of 6-Fluoronalidixic
Acid and its Conversion to Enoxacin

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1-Ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (8) has been prepared in large quantities by a highly efficient process. It has in turn been degraded to give 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11). This intermediate has been reacted with piperazine to give the known antibacterial agent, enoxacin (12).

As part of our synthetic, non-ß-lactam, antibacterial program, we required large quantities of 6-fluoronalidixic acid (8). This compound had been previously prepared in our laboratories [1] from 6-nitronalidixic acid (Equation 1), but poor and erratic yields in some of the final synthetic conversions made this route unsuitable for large scale synthesis.

Since the Balz-Schiemann reaction [2] gives variable yields, it was decided to introduce the 6-fluorine into the molecule early in the synthesis. The route outlined in Scheme I provided the early introduction of the fluorine and the other reactions in this sequence proceeded in high yield and are readily scaled up.

The diazotization of 1 [3] in 48% tetrafluoroboric acid using aqueous sodium nitrite produced the tetrafluoroborate salt 2, as a colorless crystalline solid. The thermal rearrangement of 2 in toluene afforded the fluoro compound 3 in a smooth, easily controlled reaction. The two step yield for the conversion of 1 to 3 was >90% on a two mole scale [4]. Hydrolysis of the 2-acetyl group followed by condensation with diethyl ethoxymethylenemalonate (EMME) produced the adduct 5 which could be used without further purification. The thermal ring closure of this adduct in refluxing Dowtherm-A gave 6 in 80% yield. Alkylation with ethyl iodide and potassium carbonate in hot dimethylformamide gave the ethyl ester of 6-fluoronalidixic acid (7). Mild alkaline hydrolysis of 7 provided the desired compound, 6-fluoronalidixic acid (8), in 46% overall yield from 1.

6-Fluoronalidixic acid is not only of interest in itself, but also is a key intermediate for further synthetic elaboration of the naphthyridine nucleus. Through modification of the activated methyl group [5a], 6-fluoro-7-heterocyclic analogs of nalidixic acid could be prepared [5b]. Compound 8 also provides material that could be converted by a methyl degradation procedure to 1-ethyl-6-fluoro-1,4-dihydro-7-hydroxy-4-oxo-1,8-naphthyridine-3-carboxylic acid (10b) [6a-c].

The conversion of nalidixic acid to the 7-trichloromethyl analog 9a with subsequent hydrolysis to the 7-hydroxy compound 10a has been previously reported [7]. Documentation of this oxidative perhalogenation of an activated methyl has been reported [8-9] and the hydrolysis and other reactions of this intermediate appear to be very facile.

The perhalogenation required carefully dried 6-fluoronalidixic acid (8) and redistilled thionyl chloride [10]. This step and the subsequent base hydrolysis to 10b proceeded smoothly and in high yield. The 6-fluoro-7-hydroxy compound 10b has been synthesized by several routes and its conversion to 7-chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (11) using phosphorus oxychloride is well documented [6]. The 6-fluoro-7-chloro compound 11 is very reactive toward displacement by a wide variety of nucleophiles at C-7, and a series of 7-substituted naphthyridines with potential antibacterial activity can be readily realized. Indeed, displacement with piperazine in refluxing acetonitrile produced the known antibacterial agent enoxacin (12) [6] in excellent yield.

Equation I

8
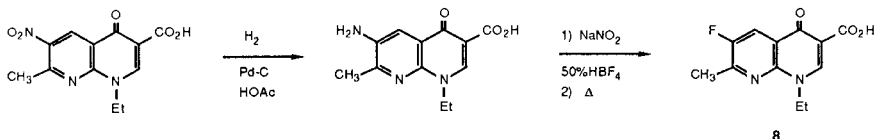
Scheme I
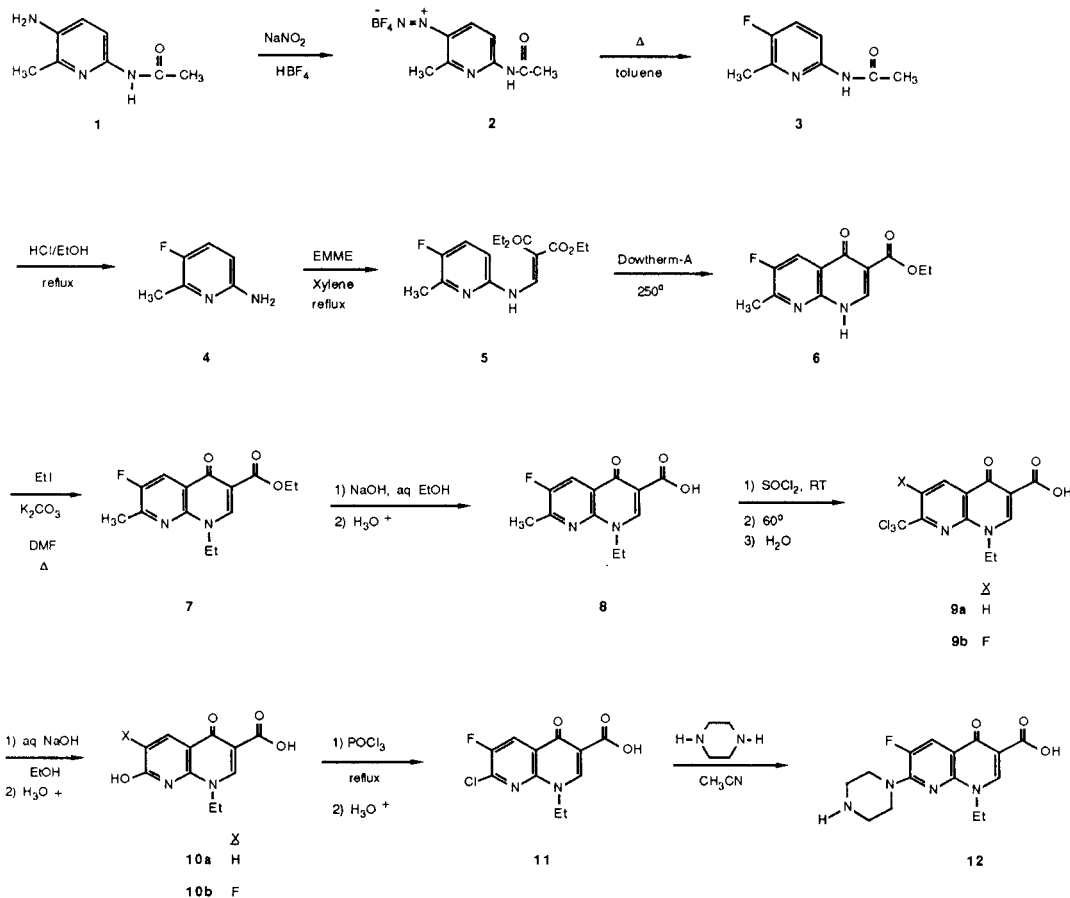
EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm⁻¹ resolution. Proton magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 30-45° and pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry nitrogen atmosphere. Elemental Analyses were performed on a Perkin-Elmer 240 elemental analyzer.

6-(Acetylamino)-2-methyl-3-pyridinediazonium Tetrafluoroborate (2).

A solution of 149.5 g (0.9 mole) of N-(5-amino-6-methyl-2-pyridinyl)acetamide (1) [3] in 500 ml of tetrafluoroboric acid was cooled to −20°, purged with nitrogen, and treated rapidly, dropwise, with a solution of 65.6 g (0.95 mole) of sodium nitrite in 125 ml of water. When the addition was complete, the reaction mixture was stirred at −10±5° for 1 hour and then diluted to 2.5 ℓ with dry ether, keeping the temperature below 0°. The precipitate was removed by filtration, washed with ether, then resuspended in ether (2 × 1.5 ℓ) (filtering between suspensions), and finally drying in vacuo to give 250.6 g (>100%) of 2 plus inorganics, decomposition range 92-96°; ir: 2230 cm⁻¹ (N₂⁺), 1735 (C=O); nmr (deu-

terium oxide): δ 2.29 (s, 3, CH₃), 2.82 (s, 3, COCH₃), 8.23 (d, J = 9 Hz, 1, Ar), 8.62 (d, J = 9 Hz, 1, Ar).

N-(5-Fluoro-6-methyl-2-pyridinyl)acetamide (3).

To a 4 liter beaker containing 2.5 ℓ of rapidly stirred toluene heated at 100° was added portionwise, 250.6 g of 6-(acetylamino)-2-methyl-3-pyridinediazonium tetrafluoroborate (2), allowing gas evolution to cease between additions. When the addition was complete the mixture was heated at mild reflux for 1 hour and then the solvent was removed in vacuo. The residue was partitioned between chloroform and 1.0 N sodium hydroxide (750 ml each). The layers were separated with the organic layer being washed with water, dried, filtered and evaporated in vacuo to give 130 g (80%) of 3, mp 142-144°; ir: 1658 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 2.18 (s, 3, COCH₃), 2.38 (d, J = 3 Hz, 3, CH₃), 7.26 (m, 1, Ar), 8.00 (m, 1, Ar), 8.17 (s, br, 1, NH).

Anal. Calcd. for C₈H₉FN₂O: C, 48.00; H, 4.53; N, 14.00. Found: C, 47.86; H, 4.70; N, 13.86.

5-Fluoro-6-methyl-2-pyridinamine (4).

A solution of 130.0 g (0.77 mole) of 3, 350 ml of 6.0 M hydrochloric acid and 400 ml of ethanol was refluxed for 6 hours. The solvent was removed in vacuo, and the residue was dissolved in water and made basic to pH 9.0 with 10% sodium hydroxide. The mixture was extracted with chloroform (3 × 400 ml); the combined chloroform layers were washed with water, dried, filtered and evaporated in vacuo to give 79 g (81%) of 4, mp 70-72°; ir: 3436 and 3308 cm⁻¹ (NH₂); nmr (deuteriochloroform): δ

2.28 (d, J = 3 Hz, 3, CH₃), 4.38 (s, br, 2, NH₂), 6.18 (m, 1, Ar), 7.10 (m, 1, Ar).

Anal. Calcd. for C₆H₇FN₂: C, 57.13; H, 5.60; N, 22.21. Found: C, 57.01; H, 5.82; N, 22.00.

Diethyl[[(5-fluoro-6-methyl-2-pyridinyl)amino]methylene]propanedioate (**5**).

A solution of 78.8 g (0.625 mole) of **4**, 151.4 g (0.7 mole) of diethyl ethoxymethylenemalonate and 1 ℓ of xylene was heated at reflux for 2 hours. The solvent was removed *in vacuo* and the hot residue (50°) was treated with 500 ml of cyclohexane and then 500 ml of petroleum ether. After an exothermic crystallization, the resulting solid was removed by filtration, washed with petroleum ether and dried *in vacuo* to give 171.6 g (93%) of **5**, mp 116-118°; ir: 3276 cm⁻¹ (NH), 1692 and 1676 cm⁻¹ (C=O); nmr (deuteriochloroform): δ 1.31 (m, 6, OCH₂CH₃), 2.42 (d, J = 3 Hz, 3, CH}), 4.20 (m, 4, OCH₂CH₃), 6.57 (m, 1, Ar), 7.18 (m, 1, Ar), 8.93 (d, J = 13 Hz, 1H, vinyl), 9.95 (d, br, J ≅ 12 Hz, 1, N-H).

Anal. Calcd. for C₁₄H₁₇FN₂O₄: C, 56.75; H, 5.79; N, 9.46. Found: C, 56.55; H, 5.94; N, 9.72.

Ethyl 6-Fluoro-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-carboxylate (**6**).

A mixture of 277.0 g (0.766 mole) of **5** and 2.0 ℓ of Dowtherm-A was heated rapidly to reflux. The ethanol that formed was removed by distillation until the temperature of the distillate reached 250°. The reaction was allowed to come to room temperature and the mixture was diluted to 5.0 ℓ with hexane. The precipitate was removed by filtration, washed with hexane, petroleum ether and air dried to give 153.0 g (80%) of **6**, mp 293-296°; ir: 1719 cm⁻¹ (C=O), 1693 (C=O); nmr (TFA-d): δ 1.58 (t, 3, OCH₂CH₃), 2.88 (d, J = 3 Hz, 3, CH₃), 4.70 (q, 2, OCH₂CH₃), 8.57 (d, J = 7 Hz, 1, C₅H), 9.47 (s, 1, Ar).

Anal. Calcd. for C₁₂H₁₁FN₂O₃: C, 57.60; H, 4.43; N, 11.20. Found: C, 57.47; H, 4.60; N, 11.22.

Ethyl 1-Ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (**7**).

A rapidly stirred mixture of 50 g (0.20 mole) of **6**, 156 g (1.0 mole) of ethyl iodide, 69.1 g (0.5 mole) of potassium carbonate and 500 ml of N,N-dimethylformamide was heated at 100° for 4.5 hours. The solvent was removed *in vacuo* and the residue was diluted with 1 ℓ of water. The resulting precipitate was removed by filtration, washed with water and dried *in vacuo* to give 53.4 g (96%) of **7**, mp 146-147°; ir: 1685 cm⁻¹ (C=O); nmr (DMSO-d₆): δ 1.39 (m, 6, OCH₂CH₃, N-CH₂CH₃), 2.62 (d, J = 2 Hz, 3, CH₃), 4.25 (q, 2, OCH₂CH₃), 4.48 (q, 2, NCH₂CH₃), 8.10 (d, J = 9 Hz, C₅H), 8.73 (s, 1, Ar).

Anal. Calcd. for C₁₄H₁₅FN₂O₃: C, 60.42; H, 5.43; N, 10.07. Found: C, 60.32; H, 5.48; N, 10.23.

1-Ethyl-6-fluoro-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**8**).

A solution of 73.0 g (0.26 mole) of **7**, 500 ml of 1.0 N sodium hydroxide and 400 ml of ethanol was heated at 100° for 1 hour and allowed to stand at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue was dissolved in water. After filtering through a fiber glass pad to clarify, the filtrate was acidified to pH 1.5 with 6.0 M hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, ethanol, ether and dried *in vacuo* to give 65.3 g (99%) of **8**, mp 252-254°; spectra and analysis were consistent with a known sample [1].

1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(trichloromethyl)-1,8-naphthyridine-3-carboxylic Acid (**9b**).

To 7.5 g (30 mmoles) of carefully dried **8** [10] was added dropwise, with stirring, 50 ml of thionyl chloride (freshly distilled from triphenyl phosphine). The reaction was stirred at room temperature for 20 minutes and then heated at 60° for 6 hours. It was then cooled to 10° and diluted to 250 ml with ether; the resulting precipitate was removed by filtration. After washing with ether and drying *in vacuo*, the yield of **9b** was 9.5 g (90%), mp 223-225°; ir: 1728 cm⁻¹ (C=O); nmr (deuteriochloroform + DMSO-d₆): δ 1.58 (t, 3, NCH₂CH₃), 4.62 (q, 2, NCH₂CH₃), 8.52 (d, J = 10 Hz, C₅H), 8.96 (s, C₂H), 12.77 (s, 1, CO₂H).

Anal. Calcd. for C₁₂H₈FCl₃N₂O₃·H₂O: C, 38.78; H, 2.71; N, 7.54. Found: C, 38.86; H, 2.62; N, 7.32.

1-Ethyl-6-fluoro-1,4-dihydro-7-hydroxy-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**10b**).

To a solution of 25 g (0.625 mole) of sodium hydroxide in 150 ml of water was added portionwise, as a dry powder, 11.3 g (32.0 mmoles) of **9b**. The reaction was stirred at room temperature for 20 minutes, heated at 100° for 2 hours, cooled to 5° and acidified to pH 2.0 with 6.0 M hydrochloric acid. The precipitate was removed by filtration, washed with water and dried *in vacuo* to give 7.8 g (98%) of **10b**, mp >300°; ir: 3460 cm⁻¹ (br, OH), 1733 cm⁻¹ (C=O); nmr (DMSO-d₆): δ 1.38 (t, 3, N-CH₂CH₃), 4.46 (q, 2, NCH₂CH₃), 8.08 (s, J = 9 Hz, 1, C₅H), 8.89 (s, 1, Ar).

Anal. Calcd. for C₁₁H₉FN₂O₄·0.4H₂O: C, 50.93; H, 3.65; N, 10.80. Found: C, 51.00; H, 3.99; N, 10.53.

7-Chloro-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**11**).

A solution of 8.5 g (33.7 mmoles) of **10** in 100 ml of phosphorus oxychloride was refluxed for 1 hour. The solvent was removed *in vacuo*, the residue triturated with ice water and the resulting solid removed by filtration. After washing with water, ethanol, ether and drying *in vacuo*, the yield of **11** was 8.9 g (98%), mp 264-266°; ir: 1723 cm⁻¹ (C=O); nmr (trifluoroacetic acid): δ 1.78 (t, 3, NCH₂CH₃), 5.07 (q, 2, NCH₂CH₃), 8.63 (d, 1, Ar), 9.56 (s, 1, Ar).

Anal. Calcd. for C₁₁H₈ClFN₂O₃: C, 48.81; H, 2.98; N, 10.35. Found: C, 49.07; H, 3.12; N, 10.52.

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